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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,324	08/23/2001	Tully Michael Underhill	3477.92	6862

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EXAMINER
DI NOLA BARON, LILIANA

ART UNIT	PAPER NUMBER
1615	13

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/856,324	Applicant(s) UNDERHILL ET AL.	
	Examiner Liliana Di Nola-Baron	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,30 and 31* is/are pending in the application.

4a) Of the above claim(s) *16,22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,17-21,24-26,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6, 11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt of Applicant's amendment, filed on June 26, 2003, is acknowledged.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-15, 17-21, 24-26 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/08546.

The patent provides pharmaceutical compositions comprising an RAR antagonist and a pharmaceutically acceptable carrier and methods comprising administering said compositions for the treatment of physical disorders, including rheumatoid arthritis (See p. 10, lines 6-27). The patent teaches that the compositions may be administered in several ways, including orally and parenterally, specifically by intraarticular injection (See p. 20, lines 13-25), and contemplates matrices of the drug in biodegradable polymers for injectable forms, and capsules, tablets, pills, powders and granules for oral administration (See p. 21, line 18-30). The patent teaches that the solid dosage forms may comprise coatings for differential release (See p. 22, lines 14-19) and the compositions may be administered in the form of liposomes (See p. 24, lines 4-12). The patent contemplates administration of the compositions in vitro, ex vivo or in vivo to cells (See p. 24, lines 14-22). In Example 1, the patent teaches that RAR antagonists does not induce RARβ2 promoter.

Thus, the patent provides pharmaceutical compositions comprising an RAR antagonist and a carrier and methods of treatment comprising administering said compositions, as claimed in the instant application. The patent is deficient in the fact that it does not specifically mention additional osteogenic factors, such as BMP, OPS, bone or collagen in the compositions of the invention, however, it contemplates administering said compositions in combination or coincidental with other drugs (See p. 24, line 27 to p. 25, line 11), thus, one of ordinary skill in the art would have combined the RAR antagonist with additional osteogenic factors to obtain a more efficacious treatment.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of the patent to device pharmaceutical compositions and methods of treatment comprising administering said compositions, and include in said compositions additional drugs or osteogenic factors for the development of bones. The expected result would have been a successful pharmaceutical composition and successful methods of treatment. Because of the teachings of the patent, that the compositions of the invention can be administered, in vitro, ex vivo or in vivo in various forms and may be used for the treatment of arthritis, one of ordinary skill in the art would have a reasonable expectation that the compositions and methods claimed in the instant application would be successful. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

3. Claims 1-15, 17-21, 24-26 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Basset et al. (U.S. Patent 6,184,256).

The patent provides pharmaceutical compositions comprising an RAR antagonist and a pharmaceutically acceptable carrier and methods comprising administering said compositions for the treatment of physical disorders, including arthritis and osteoporosis (See col. 8, line 16 to col. 9, line 19). The patent teaches that the compositions may be administered in several ways, including orally and parenterally, specifically by intraarticular injection (See col. 20, lines 11-37), and contemplates matrices of the drug in biodegradable polymers for injectable forms and capsules, tablets, pills, powders and granules for oral administration (See col. 21, lines 9-42). The patent teaches that the solid dosage forms may comprise coatings for differential release (See col. 21, lines 47-59) and the compositions may be administered in the form of liposomes (See col. 22, lines 57-59). The patent contemplates administration of the compositions in vitro, ex vivo or in vivo to cells (See col. 23, lines 6-19).

Thus, the patent provides pharmaceutical compositions comprising an RAR antagonist and a carrier and methods of treatment comprising administering said compositions, as claimed in the instant application. The patent is deficient in the fact that it does not specifically mention additional osteogenic factors, such as BMP, OPS, bone or collagen in the compositions of the invention, however, it contemplates administering said compositions in combination or coincidental with other drugs (See col. 23, lines 32-40), thus, one of ordinary skill in the art would have combined the RAR antagonist with additional osteogenic factors to obtain a more efficacious treatment.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of the patent to device pharmaceutical compositions and methods of treatment comprising administering said compositions, and include in said compositions additional drugs or osteogenic factors for the development of bones. The expected result would have been a successful pharmaceutical composition and successful methods of treatment. Because of the teachings of the patent, that the compositions of the invention can be administered, in vitro, ex vivo or in vivo in various forms and may be used for the treatment of arthritis, one of ordinary skill in the art would have a reasonable expectation that the compositions and methods claimed in the instant application would be successful. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

4. Claims 2-4 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bollag et al. (U.S. Patent 6,326,397).

The patent provides compositions comprising retinoid antagonists and a carrier for the treatment of patients suffering from osteoporosis or arthritis, and teaches that retinoid antagonists increase bone formation, which is a function of osteoblasts that build up the matrix comprising type I collagen and proteins (See col. 7, line 17 to col. 9, line 49). The patent contemplates combining the retinoid antagonists with other active substances into one pharmaceutical composition and teaches that the compositions may be administered orally, in the form of tablets, pills or granules (See col. 11, lines 17-63).

Thus, the patent provides pharmaceutical compositions comprising an RAR antagonist and a carrier and methods of treatment comprising administering said compositions, as claimed in the instant application. The patent is deficient in the fact that it does not specifically mention additional osteogenic factors, such as BMP, OPS, bone or collagen in the compositions of the invention, however, it contemplates administering said compositions in combination with other drugs (See col. 11, lines 17-26), and teaches that bone formation depends on osteoblasts that build up the matrix comprising type I collagen and proteins, thus, one of ordinary skill in the art would have combined the RAR antagonist with additional osteogenic factors, specifically type I collagen and osteogenic proteins, to obtain a more efficacious treatment.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of the patent to device pharmaceutical compositions and include in said compositions additional drugs or osteogenic factors for the development of bones. The expected result would have been a successful pharmaceutical composition. Because of the teachings of the patent, that the compositions of the invention are effective in the treatment of arthritis and osteoporosis, one of ordinary skill in the art would have a reasonable expectation that the compositions claimed in the instant application would be successful. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

5. Applicant's arguments filed June 26, 2003 have been fully considered but they have been found only partially persuasive.

6. Applicant's argument with regard to the priority claim has been found persuasive. Accordingly, foreign priority will be considered for all pending claims.

7. Applicant's information disclosure statement, filed March 31, 2003 has been considered.

8. Applicant's abstract of the disclosure has been placed in the application file.

9. Applicant's amendment has overcome the 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph rejection of claims 9-11 of the previous Office action. Accordingly, said rejection is withdrawn.

10. Applicant argues that WO 98/08546 is silent with respect to the use of a composition of a RAR antagonist, without any agonist, for inducing chondrogenesis. In response to said argument, it is noted that the "comprising" language in the instant claims allows for the presence of additional active agents in the compositions disclosed by the prior art. Furthermore, with regard to composition claims 1-8, the limitation "wherein said composition induces chondrogenesis or chondrogenesis and related skeletal development in a vertebrate" is a feature intended use, and, as such, does not have patentable weight in composition claims. With regard to the methods claimed in claims 9-11 and 17-25 of the instant application, the international application teaches that the compositions and methods of the invention may also be used to treat an animal suffering from other physical disorders that respond to treatment with retinoids (See p. 19, lines 21-23). Thus, one of ordinary skill in the art would have been motivated to device methods as claimed in the instant application, in view of the prior art, that teaches that retinoic acid is known to regulate

the proliferative and differentiative capacities of several mammalian cell types (See p. 8, lines 13-14).

11. Applicant argues that Basset et al. is silent as to the use of an RAR antagonist for the stimulation of chondrogenesis or the treatment of any disorder requiring chondrogenesis for its treatment. In response to said argument, it is noted that the patent provides pharmaceutical compositions comprising an RAR antagonist and a pharmaceutically acceptable carrier and methods comprising administering said compositions for the treatment of physical disorders, including arthritis and osteoporosis (See col. 8, line 16 to col. 9, line 19). Arthritis and osteoporosis require chondrogenesis for treatment.

12. Applicant argues that Bollag et al. is silent as to the use of an RAR antagonist for the stimulation of chondrogenesis. In response to said argument, it is noted that the patent provides compositions comprising retinoid antagonists and a carrier for the treatment of patients suffering from osteoporosis or arthritis, and teaches that retinoid antagonists increase bone formation (See col. 7, line 17 to col. 9, line 49).

Conclusion

13. Claims 1-15, 17-21, 24-26, 30 and 31 are rejected.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liliana Di Nola-Baron whose telephone number is 703-308-8318. The examiner can normally be reached on Monday through Thursday, 5:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 308-1234/ 1235.

LDN83

September 16, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600